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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/981,286 | 10/15/2001 | Stanley J. Watowich | 265.00260101 | 4993 |

7590 05/20/2003

Attention: David L. Provence
Mueting, Raasch, & Gebhardt, P.A.
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| EXAMINER |
|---|
| ZHOU, SHUBO |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1631 | |

DATE MAILED: 05/20/2003 18

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/981,286 | Applicant(s) WATOWICH ET AL. | |
|---|---|---|---|
| | Examiner Shubo "Joe" Zhou | Art Unit 1631 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *3/26/03, and 4/25/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *1-24 and 30-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-29* is/are rejected.

7)☒ Claim(s) *25-29* is/are objected to.

8)☒ Claim(s) *1-34* are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 October 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *15 February 2002* is: a)☐ approved b)☒ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

**DETAILED ACTION**

Applicant's election with traverse of Group VIII (claims 25-29) and of species "Vero cells" in Paper No. 15, filed 3/26/03, is acknowledged. The traversal is on the ground(s) that all the invention groups can be readily evaluated in one search without placing undue burden on the Office. See page 2. This is not found persuasive because, as set forth in the previous Office action, mailed 2/27/03, the nine groups of inventions, as detailed on page 2-3, are classified differently and drawn to separate/distinct inventions. Further, they are most commonly separately characterized and published in the biomedical literature. As such, co-examination of all the groups by the Office would require searching the different inventions in different classifications of the US patents and different subject matter in the literature, and would require different search strategy for each of the inventions, which clearly would be an undue burden on the Office.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, only claims 25-29 are under consideration. Claims 1-24, and 30-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 15.

Per the telephone interview conducted between the Examiner and David Provence on 4/25/03, applicants filed amendment to claim 25 in Paper #17 on 4/25/03 to clarify confusion in amino acid number recitation in the claim. The amendment is entered.

Additionally, the preliminary amendment in Paper #7, filed on 2/15/02, is also acknowledged and entered.

## *Information Disclosure Statement*

The Information Disclosure Statement filed 8/1/02 has been entered and considered. Initialed copies of the form PTO-1449 are enclosed with this action.

## *Specification*

The title of the invention is not descriptive. The current title is simply "Drug Discovery Methods" whereas the elected invention is drawn to a method of identifying polypeptides that prevent cell death after exposure of the cell to a pathogen or toxin, which is not drug discovery. A new title is requested that is clearly indicative of the invention to which the elected claims are directed.

The disclosure is objected to because of the following informalities:

In the Brief Description of the Figures section of the specification, Figure 2 is referred to. However, the drawings filed do not have Figure 2, but only Figure 2A, Figure 2B and Figure 2C.

The sentence in lines 28-29 does not end with a punctuation mark.

On page 2 of the specification, it is stated:

> "Each polypeptide includes a fragment of SEQ ID NO:1 beginning at any amino acid from about 119 to about 124 and ending at any amino acid regions of amino acid from about 258 to about 275 ... or amino acids 257-264 as depicted at SEQ ID NO:1..."

The statement is confusing because SEQ ID NO:1 is an amino acid sequence of only 156 amino-acid long. However, through the description for Figure 1 in the specification (page 6), it appears that the sequence of residues 1-156 of SEQ ID NO:1 is a fragment of, and is the same as that of residues 119-275 of the VEE virus capsid polypeptide. So, residues 119-275 are meant to

be consistent with the numbering of the amino acids for the VEE virus capsid polypeptide. Similar confusing statements also appear on pages 3, 8, etc. Appropriate correction is requested to clarify the confusion.

Appropriate correction is required.

## *Drawings*

The proposed drawing correction filed on 2/15/02, has been disapproved because it is not in the form of a pen-and-ink sketch showing changes in red ink or with the changes otherwise highlighted. See MPEP § 608.02(v).

It is noted that the proposed correction was intended to add sequence identifiers to sequences in Fig. 2B and Fig. 2C to comply with the requirements of 37 C.F.R. 1.821 through 1.825. Since the proposed correction is not approved, the requirements of 37 C.F.R. 1.821 through 1.825 are not fully complied with due to the absence of a sequence identifier for the sequences in the figures. Thus, the amendments are still required in order to comply with the sequence rules. Alternatively, however, applicants are reminded that sequence identifier ("SEQ ID NO:X") for the sequences can be added in the Brief Description of the Drawings section of the specification.

The drawings filed 10/15/01 are objected to by the Draftsperson under 37 CFR 1.84 or 1.152 for the reasons detailed on Form PTP-948, which is attached. Applicants are reminded that the required timing for the correction of drawings has changed. See 37 CFR 1.85 and the backside of the Notice of Draftsperson's Patent Drawing Review. Applicants are required to submit drawing corrections within the time period set for responding to this Office action.

Failure to respond to this requirement may result in abandonment of the instant application or a notice of a failure to fully respond to this Office action.

## *Claim Rejections-35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

**Claims 25-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.**

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)), the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation; (b) the amount of guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the predictability of the art; (g) the breadth of the claims; and (h) the relative skill in the art. The factors are analyzed for the instant case as follows:

(a) In the instant case, the amount of experimentation required by a skilled artisan in order to practice using the claimed method to identify a polypeptide that prevents cell death after

exposure of the cell to a pathogen or toxin would require an unpredictable amount of experimentation for the following reasons:

(b) There is no guidance in the instant specification that teaches the skilled artisan how to use the claimed methods to identify a polypeptide comprising a fragment of VEE capsid protein that prevents cell death after exposure of the cell to a pathogen or toxin. While the specification indeed provides guidance to making a collections of polypeptides comprising a fragment of the VEE capsid protein and introduce them into cells, it fails to provide sufficient guidance with respect to the structures, especially conformations, and properties of the polypeptides, neither does it provide guidance as to the structures and components of pathogens or toxins, as well as their potential interactions with the collection of polypeptides, which are all critical factors for successfully identifying a polypeptide comprising a fragment of VEE capsid protein that prevents cell death after exposure of the cell to a pathogen or toxin.

(c) The instant application does not present any working examples wherein the claimed methods are used to have actually identified a polypeptide from a collection of polypeptides comprising a fragment of VEE capsid protein that prevents cell death after exposure of the cell to a pathogen or toxin.

(d) The nature of the invention, a method for identifying a polypeptide from a collection of polypeptides comprising a fragment of VEE capsid protein that prevents cell death after exposure of the cell to any pathogen or any toxin, is complex, especially given the extreme diversity of pathogens and toxins and the high complexity of the structures and properties thereof. For example, a pathogen can be a multi-cellular organism, a unicellular bacteria, a virus, or any substance that causes a disease (Stedman's Online Medical Dictionary, 27th Edition,

**pathogen:** Any virus, microorganism, or other substance causing disease), and a toxin may have any chemical structure and exert its effect in any may or form (Stedman's Online Medical Dictionary, 27th Edition, **toxin:** A noxious or poisonous substance that is formed or elaborated either as an integral part of the cell or tissue, as an extracellular product (exotoxin), or as a combination of the two, during the metabolism and growth of certain microorganisms and some higher plant and animal species).

(e) The prior art does not teach or suggest the claimed invention: displaying a collection of fusion polypeptides of a fragment of VEE capsid protein with other random polypeptides in vivo, exposing a cell comprising such fusion polypeptides to pathogens or toxins, and identifying a polypeptide from the collection that prevents the death of the cell. The prior art does teach displaying certain fusion polypeptides in vivo and identifying polypeptide that disturbs a particular cellular pathway. For example, Caponigro et al. (Proc. Natl. Acad. Sci. USA, Vol. 95, pages 7508-7513, June 1998) teach using the green fluorescent protein (GFP) as a scaffold to display peptides *in vivo* and screening for peptide that inhibits the pheromone response pathway in yeast. See the entire document, especially pages 7508-7511. Norman et al. (Science, Vol. 285, pages 591-595, July 1999) teach using a highly expressed and biologically inert carrier protein derived from staphylococcal nuclease to display random peptides in vivo and selecting peptide that inhibits the pheromone signaling pathway, transcriptional silencing and the spindle checkpoint. Further, Norman et al. stress the importance of maximum expression of the random polypeptides in vivo (see page 591) and the requirement of a reliable test for verifying the potential candidates because of the very high rate of false positives and false negatives. See page 594.

(f) The prior art does not address predictability with regard to a successful identification of a polypeptide from a collection of polypeptides displayed in vivo that inhibits cell death after exposure of the cell to a pathogen or toxin. In general, the prior art does not address the predictability of identifying a polypeptide that inhibits a particular biological or cellular pathway.

(g) The claim to a method of identifying a polypeptide from a collection of polypeptides comprising a fragment of VEE capsid protein that inhibits cell death after exposure of the cell to a pathogen or toxin in claim 25 is broad because it can be any polypeptide comprising a fragment of VEE capsid protein as required in the claim and it can be any pathogen or any toxin, which possesses broad range of structures and properties. Even for the dependent claims 26-29, they are also broad in that there is a great amount of different viruses or microbe (claim 26), bacterium, rickettsia or fungus (claim 27), biological toxins (claim 28) or chemical toxins (claim 29).

(h) The level of skill of those in the art who practice identifying a polypeptide from a collection of polypeptides displayed in vivo that inhibits a particular biological or biochemical pathway is high.

The skilled practitioner would first turn to the instant specification for guidance in practicing a method to identify a polypeptide from a collection of polypeptides comprising a fragment of VEE capsid protein displayed in vivo, that inhibits cell death after exposure of the cell to a pathogen or toxin, as claimed. However, the specification does not provide sufficient guidance for successfully practicing the method as claimed to achieve its objective, i.e. obtaining a polypeptide comprising a fragment of the VEE capsid protein that inhibits cell death in response to a pathogen or toxin. As such, the skilled practitioner would turn to the prior art for such guidance. However, the prior art does not teach or suggest the means to practice a method

for identify a polypeptide from a collection of polypeptides comprising a fragment of VEE capsid protein displayed in vivo, that inhibits cell death after exposure of the cell to a pathogen or toxin, as claimed. Finally, said practitioner would have to turn to trial and error experimentation to identify a polypeptide comprising a fragment of the VEE capsid protein that inhibits cell death in response to a pathogen or toxin, without guidance from the specification or the prior art. Therefore, undue experimentation becomes the burden of the practitioner.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

**Claims 25-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

The limitation "beginning at any amino acid from about 119 to about 124 and ending at any amino acid from about 258 to about 275" in claim 25 is vague and confusing. It is unclear what the phrase modifies, i.e. what is "beginning ... and ending...", the "each polypeptide", the "fragment" or the "Venezuelan equine encephalitis (VEE) virus capsid polypeptide". Thus, the metes and bounds of the claim are not clear.

Claims 26-29 are rejected due to their dependency from claim 25 and thus also containing the confusing limitation.

## *Claim Objections*

Claims 25-29 are objected to because of the following informalities:

The phrase "Venezuelan equine encephalitis virus (VEE) virus capsid polypeptide" in claim 25 is awkward for the use of two "virus" words. Does applicant intend to mean "Venezuelan equine encephalitis (VEE) virus capsid polypeptide"?

Claims 26-29 are objected to due to their dependency from claim 25 and thus containing the same limitation.

Appropriate correction is required.

## *Conclusion*

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to:
Shubo "Joe" Zhou, Ph.D., whose telephone number is (703) 605-1158. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst Tina Plunkett whose telephone number is 703)-305-3524, or to the Technical Center receptionist whose telephone number is (703) 308-0196.

Shubo "Joe" Zhou, Ph.D.
Patent Examiner